LETTERS 2005 Vol. 7, No. 7 1431–1434

ORGANIC

Highly *Exo*-Selective and Enantioselective Cycloaddition Reactions of Nitrones Catalyzed by a Chiral Binaphthyldiimine–Ni(II) Complex

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Received February 23, 2005





Significant levels of *exo*-selectivity (*exo*:*endo* = >99:1 to 86:14) and enantioselectivity (95–82% ee) were obtained in the 1,3-dipolar cycloadditions of a number of nitrones with 3-(2-alkenoyl)-2-thiazolidinethiones, using the chiral binaphthyldiimine–Ni(II) complex (5–20 mol %), which was easily prepared form *N*,*N*'-bis(3,5-dichrolo-2-hydroxybenzylidene)-1,1'-binaphthyl-2,2'-diamine and Ni(ClO₄)₂-6H₂O in CHCl₃ in the presence of 4 Å molecular sieves, as a chiral Lewis acid catalyst.

Asymmetric 1,3-dipolar cycloaddition reactions between nitrones and alkenes are among the most efficient methods for the construction of optically active isoxazolidines, which are readily converted to synthetically useful chiral γ -amino alcohols (Scheme 1).¹ Recently, a number of chiral Lewis acids have been shown to possess high enantioselectivity in the reactions of nitrones with electron-rich and -deficient olefins.^{1a-d} For the reactions of electron-deficient alkenes, 3-(2-alkenoyl)-2-oxazolidinones often have been employed as the dipolarophiles to yield, in most cases, the *endo*-cycloadducts with high enantioselectivity.^{2,3} On the other hand, the efficient synthesis of enantiomerically pure γ -amino alcohols having a *syn,anti* diastereomeric structure via nitrone

cycloaddition reactions would require a chiral Lewis acid that favors the *exo*-selective and enantioselective cycloadditions (Scheme 1). For example, a formal synthesis of thienamycin and a key intermediate synthesis of carbapenems with the enantiomerically pure $syn,anti-\gamma$ -amino alcohols, which were obtained from the cycloaddition reactions of



⁽¹⁾ For recent reviews, see: (a) Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry toward Heterocycles and Natural Products; Padwa, A., Pearson, W. H., Eds.; John Wiley and Sons: Hoboken, NJ, 2003. (b) Gothelf, K. V.; Jørgensen K. A. Chem Commun. 2000, 1449. (c) Gothelf, K. V.; Jørgensen, K. A. Chem. Rev. 1998, 98, 863. (d) Frederickson, M. Tetrahedron 1997, 53, 403. (e) 1,3-Dipolar Cycloaddition Chemistry; General heterocyclic chemistry series; Padwa, A., Ed.; John Wiley and Sons: New York, 1984; Vol. 2, pp 83–168.

nitrones attached to a chiral auxiliary with crotonate ester, were reported.⁴ To date, however, only a few examples of the exo-selective cycloadditions of nitrones with 2-alkenoic acid derivatives in the presence of a chiral Lewis acid have been reported.5 More recently, Sibi has reported on highly exo-selective cycloadditions that also possess high enantioselectivity using the chiral relay in reactions with 2-(2alkenoyl)-3-pyrazolidinones as the dipolarophiles.^{5f} This procedure, however, remains problematic in terms of the catalyst loading (30-50 mol %) and the generality of nitrones. In this Letter, we report on a facile methodology for the highly exo-selective and enantioselective cycloaddition reactions between various nitrones and 3-(2-alkenoyl)-2-thiazolidinethiones in the presence of a chiral binaphthyldiimine (BINIM)-Ni(II) complex^{5e,6} (5-20 mol %) as the Lewis acid catalyst.

On the basis of our previous investigations of the stereoselectivity of cycloaddition reactions between nitrones and 3-crotonoyl-2-oxazolidinone catalyzed by BINIM-Ni(II) complexes,^{5e} cycloaddition reactions between *N*-benzylideneaniline *N*-oxide (**1a**) and 3-crotonoyl-2-thiazolidinethione (**2a**) in the presence of BINIM-Ni(II) complexes (10 mol %) were initially examined (Scheme 2 and Table 1). These



complexes were prepared from several BINIM ligands (see Figure 1) and Ni(ClO₄)₂·6H₂O in the presence of 4 Å molecular sieves (MS 4A). Surprisingly, for almost all BINIM ligands that were tested, the *exo*-cycloadduct was

 Table 1.
 BINIM-Ni(II)-Catalyzed Enantioselective

 Cycloadditions of Nitrone 1a with

 2.
 Cycloadditions of Nitrone 1a with

3-Crotonoyl-2-thiazolinethione	$(2a)^{a}$
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entry	BINIM	solvent	time (h)	yield (%)	exo:endo ^b	ee ^c (%)
1	(R)-BINIM-DC	CH_2Cl_2	24	59	62:38	-31
2	(R)-BINIM-2QN	CH_2Cl_2	80	83	58:42	89
3	(R)-BINIM-4Me-2QN	CH_2Cl_2	64	66	72:28	91
4	(R)-BINIM-4Ph-2QN	CH_2Cl_2	72	86	59:41	90
5	(S)-BINIM-OH	CH_2Cl_2	115	26	97:3	-25
6	(R)-BINIM-5ClOH	CH_2Cl_2	20	40	98:2	-29
7	(R)-BINIM-DBOH	CH_2Cl_2	30	77	97:3	88
8	(R)-BINIM-DCOH	CH_2Cl_2	15	93	98:2	90
9	(R)-BINIM-DCOH	THF	48	77	91:9	74
10	(R)-BINIM-DCOH	Toluene	40	90	98:2	83
11	(R)-BINIM-DCOH	$CHCl_3$	15	87	>99:1	93

^{*a*} The reaction was carried out in the presence of BINIM–Ni(II) catalyst (10 mol %), which was prepared by mixing BINIM, Ni(ClO₄)₂•6H₂O, and MS 4A in the corresponding solvent, at room temperature. ^{*b*} Determined by ¹H NMR. ^{*c*} Enantiomeric excess (ee) of the *exo*-adduct was determined by HPLC.

preferably obtained when thiazolidinethione **2a** was used as a dipolarophile. Although the *exo*-selectivities were unsatisfactory, quinoline-based BINIM—Ni(II) catalysts showed high enantioselectivities toward the *exo*-cycloadducts (entries 2–4). Interestingly, when 2-hydroxybenzylideneamine-type ligands were used in combination with **2a** as a dipolarophile, high *exo*-selectivities were observed (entries 5–8). Furthermore, the use of BINIM-DCOH or BINIM-DBOH indicated promising levels of asymmetric induction with extremely high *exo*-selectivities (entries 7 and 8). For the BINIM-DCOH—Ni(II)-catalyzed reactions, a survey of the reaction solvents (entries 9–11) revealed that CHCl₃ provided the most favorable results in terms of *exo*-selectivity (>99:1) and enantioselectivity (93% ee) (entry 11).

The optimized conditions with (R)-BINIM-DCOH were subsequently applied to reactions between various nitrones and 3-crotonoyl-2-thiazolidinethione (2a) (Scheme 2 and Table 2). Regardless of the electron-donating or -attracting character of the *p*-substituents on the *N*-benzene ring, high *exo*-selectivities (93:7 - >99:1) and high enantioselectivities (88-95% ee) were observed in the reactions of several C-phenyl-N-p-substituted phenyl nitrones (1b-e, entries 2-4 and 6). It should be noted that the reactions of nitrones 1a and 1d with 2a in the presence of 5 mol % of the (R)-BINIM-DCOH-Ni(II) complex afforded the products in good yields with extremely high exo-selectivities and enantioselectivities (entries 1 and 5).⁷ The cycloaddition reactions of C-psubstituted phenyl-N-phenyl nitrones 1f-h and C,N-bis(pchlorophenyl)nitrone 1i with 2a in the presence of (R)-BINIM-DCOH-Ni(II) complex (10 mol %) also showed

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Table 2. BINIM-DCOH-Ni(II)-Catalyzed EnantioselectiveCycloadditions of Nitrones 1a-l with

3-(2-Alkenoyl)-2-thiazolinethiones 2a-da

	nitrone			2	time	vield	exo:	eec
entry	\mathbb{R}^1	\mathbb{R}^2	1	Ē	(h)	(%)	$endo^b$	(%)
1^{d}	Ph	Ph	1a	Me	69	70	99:1	90
2	$p-{ m MeC_6H_4}$	Ph	1b	Me	19	78	93:7	88
3	$p-MeOC_6H_4$	Ph	1c	Me	22	36	>99:1	>90
4	p-ClC ₆ H ₄	Ph	1d	Me	15	98	>99:1	95
5^d	p-ClC ₆ H ₄	Ph	1d	Me	64	80	>99:1	95
6	p-BrC ₆ H ₄	Ph	1e	Me	20	90	98:2	92
7	Ph	$p-{ m MeC_6H_4}$	1f	Me	41	78	>99:1	93
8	Ph	$p-MeOC_6H_4$	1g	Me	48	92	99:1	92
9	Ph	p-ClC ₆ H ₄	1h	Me	60	85	>99:1	95
10	p-ClC ₆ H ₄	p-ClC ₆ H ₄	1i	Me	60	85	98:2	93
11	Bn	Ph	1j	Me	78	60	93:7	90
12	Me	Ph	1k	Me	117	68	86:14	85
13^{f}	Bn	\mathbf{Et}	1l	Me	96	42	90:10	82
14	Ph	Ph	1a	\mathbf{Et}	52	74	97:3	91
15	p-ClC ₆ H ₄	Ph	1d	\mathbf{Et}	15	73	93:7	91
16	Ph	$p-MeOC_6H_4$	1g	\mathbf{Et}	98	49	>99:1	83
17	Ph	p-ClC ₆ H ₄	1h	\mathbf{Et}	64	64	94:6	92
18	Ph	Ph	1a	n-Pr	45	73	99:1	91
19	p-ClC ₆ H ₄	Ph	1d	n-Pr	45	75	>99:1	93
20	Ph	p-ClC ₆ H ₄	1g	n-Pr	70	95	>99:1	90
21	Ph	Ph	1a	\mathbf{Ph}	150	35	>99:1	87^{e}
22^{f}	Ph	Ph	1a	Ph	69	59	>99:1	87^{e}

^{*a*} The reaction was carried out in the presence of BINIM-DCOH–Ni(II) (10 mol %), which was prepared by mixing (*R*)-BINIM-DCOH, Ni(ClO₄)₂· 6H₂O, and MS 4A in CHCl₃ at room temperature. ^{*b*} Determined by ¹H NMR. ^{*c*} Enantiomeric excess (ee) of the *exo*-adduct was determined by HPLC. ^{*d*} 5 mol % of catalyst was used. ^{*e*} Determined by ¹H NMR after conversion to diastereomeric amides of (*R*)-(+)- α -methylbenzylamine. ^{*f*} 20 mol % of catalyst was used.

The absolute configuration of the cycloadduct **3a** obtained from nitrone **1a** and olefin **2a** was determined after conversion to the corresponding 4-hydroxymethylisoxazolidine by NaBH₄ reduction. Thus isoxazolidine **3a** (90% ee by HPLC) obtained from the above reaction was treated with NaBH₄ in THF–water to give alcohol **4a** (92% ee by HPLC) possessing 3R,4S,5S configuration, which was determined by comparison with the sign of specific rotation in the literature ($[\alpha]^{25}_{D}$ +176.0 (*c* 1.0, CHCl₃), (3R,4S,5S), 99% ee),^{5f} in 53% yield (Scheme 3). Therefore, the absolute



configuration of the cycloadduct 3a was assigned as 3R, 4R, 5S. The other cycloadducts were also presumed to have the same absolute configuration.

Although the detailed structure of the catalyst remains unclear,⁹ it is apparent that 2-hydroxybenzylideneamine moiety of the BINIM ligands in the Ni(II) complexes in conjunction with 3-(2-alkenoyl)-2-thiazolidinethiones as di-



Figure 1. Structures of chiral binaphthyldiimine ligands.

satisfactory results in terms of *exo*-selectivities (98:2 - >99:1) and enantioselectivities (92-95% ee) (entries 7-10), and were independent of the electronic character of the *p*-substituents of the *C*-benzene ring.

It is noteworthy that the catalytic activities of (*R*)-BINIM-DCOH-Ni(II) catalyst can be extended to *N*-alkyl nitrones **1j** and **1k** and *C*,*N*-dialkyl nitrone **1***l* with good *exo*selectivities and enantioselectivities (entries 11, 12, and 13). This chiral Ni(II) catalytic system was also applicable to 1,3dipolar cycloaddition reactions of several nitrones with 3-(2pentenoyl)- (**2b**), 3-(2-hexenoyl)- (**2c**), and 3-cinnamoyl-2thiazolidinethione (**2d**) with satisfactory *exo*-selectivities and enantioselectivities (entries 14-22). Although 20 mol % catalyst was needed in the cases of the reactions of nitrone **11** with olefin **2a** and nitrone **1a** with olefin **2d** for moderate yield (entries 13 and 22), catalytic activity of the BINIM-Ni(II) complex is noteworthy because these reactions under reflux in toluene or with Sc(OTf)₃ as a Lewis acid gave almost no cycloadducts.⁸

⁽⁷⁾ For the reaction of 1d, decreasing the catalyst loading to 1 or 2 mol % (rt for 112 h) resulted in lower yields (36% and 50%, respectively) and enantioselectivity (62% ee and 83% ee, respectively), but with high *exo*-selectivity (95:5 and 97:3, respectively).

⁽⁸⁾ Reaction of **1***l* with **2a**: reflux in toluene for 23 h, trace; $Sc(OTf)_3$ (10 mol %) in CH₂Cl₂ for 160 h, 0% yield. Reaction of **1a** with **2d**: reflux in toluene for 20 h, 0% yield.

polarophiles is extremely important for unusual *exo*-selectivity in the Lewis acid-catalyzed cycloaddition reactions of nitrones. We also revealed that halogen atoms substituted at the 3-position on benzene rings in the 2-hydroxyphenyl-based BINIM ligands played an important role for high enantioselectivity. The sufficient improvement of enantioselectivity and somewhat different ligand dependence on *exo*-selectivity utilizing 3-(2-alkenoyl)-2-thiazolidinethiones as dipolarophiles compared with using 3-crotonyl-2-oxazolidinone are probably due to longer and more suitable bond lengths of Ni-S and S=C than those of Ni-O and O=C in the BINIM-Ni(II)-catalyzed cycloaddition reactions of nitrones. In conclusion, highly *exo*-selective and enantioselective

1,3-dipolar cycloaddition reactions between nitrones and

3-(2-alkenoyl)-2-thiazolidinethiones were carried out by using (*R*)-BINIM-DCOH—Ni(II) as a chiral Lewis acid catalyst. In contrast to other chiral Lewis acids that have been reported for nitrone cycloadditions, it is noteworthy that our methodology offers extremely high *exo*-selectivity along with high enantioselectivity for a number of nitrones. Furthermore, only the catalyst loading as small as 5-10 mol % was active enough in most cases.

Acknowledgment. This work was supported in part by a Grant-in-Aid for Scientific Research (No. 15550087) from the Ministry of Education, Science and Culture, Japan.

Supporting Information Available: Representative experimental procedures and spectroscopic data of the reaction products. This material is available free of charge via the Internet at http://pubs.acs.org.

OL050397H

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